

Single oral dose of cefaclor for the treatment of infections with penicillinase-producing strains of *Neisseria gonorrhoeae*

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SUMMARY A single oral dose of 3 g cefaclor was effective in the treatment of uncomplicated gonococcal infection in women due to penicillinase-producing strains of *Neisseria gonorrhoeae* (PPNG). Cefaclor was equally active in vitro against both PPNG (MIC range, 0.01-1.0 µg/ml) and non-PPNG strains (MIC range, 0.005-2.0 µg/ml). As empirical treatment cefaclor was effective in 53 of 57 (93%) patients compared with ampicillin, to which only 37 of 53 (69.8%) patients responded. This difference was attributed to the 40% incidence of PPNG in the patients studied; as expected, such patients responded poorly to ampicillin.

Introduction

Cefaclor is an acid-stable semisynthetic cephalosporin which differs from its parent substance, cephalexin, in the substitution of a chloro group in the 3 position. Like cephalexin, cefaclor is absorbed orally but has the advantage of greater in-vitro activity against pathogens, particularly *Haemophilus influenzae* and *Neisseria gonorrhoeae* and their β -lactamase-positive strains.^{1,2} Compared with other cephalosporins cefaclor was second only to cefuroxime in its activity against *N gonorrhoeae*.²

Preliminary studies of the treatment of gonococcal urethritis in men have shown cefaclor to be effective in doses ranging from 2-4 g with or without probenecid.³ Its efficacy in infections with penicillinase-producing *N gonorrhoeae* (PPNG) has not yet been studied. The purpose of this study was to determine the efficacy of cefaclor in the treatment of uncomplicated gonococcal infections in women, particularly those due to PPNG. The results of empirical treatment of gonococcal infection with this drug were compared to those with the standard oral dose of ampicillin. Minimum inhibitory concentrations (MIC) of cefaclor, ampicillin, and penicillin against the isolates of *N gonorrhoeae* were measured and correlated with the response to treatment.

Patients and methods

STUDY DESIGN

Prostitutes with uncomplicated gonococcal infection confirmed by culture on screening volunteered to join the study after the protocol had been explained. Written informed consent was obtained and the study was conducted in accordance with the guidelines for human experimentation of the Declaration of Helsinki and the Committee on Research, Ethics, and Development of the UP Health Sciences Center.

Pretreatment culture specimens were obtained from the cervix, urethra, rectum, and pharynx, after which patients were assigned to either treatment group by random allocation using a table of random numbers.

The patients were admitted to the clinic for three days after treatment to observe for possible side effects and, more importantly, to preclude reinfection before test-of-cure cultures were obtained on the second and third post-treatment days. Only patients with confirmed gonococcal infection based on a positive pretreatment culture result were evaluated. Treatment was considered to have failed if post-treatment culture results were still positive for *N gonorrhoeae*.

TREATMENT REGIMENS

Treatment consisted of a single oral dose of either 3 g cefaclor or 3.5 g ampicillin with 1 g probenecid. Patients who were randomly allocated to the ampicillin group and from whose pretreatment cultures PPNG were subsequently isolated were retreated

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with spectinomycin 2g intramuscularly after post-treatment culture results were obtained and immediately before discharge.

STATISTICAL ANALYSIS

Fisher's exact test and the χ^2 test with Yates's correction were used.

BACTERIOLOGICAL TECHNIQUES

N gonorrhoeae was isolated and identified according to standard procedures.⁴ Penicillinase production by the isolated strains of *N gonorrhoeae* was determined by the rapid iodometric test⁵ and confirmed by the chromogenic cephalosporin method of O'Callaghan.⁶ The MICs of cefaclor, ampicillin, and penicillin were determined by the agar dilution method using standard procedures.⁷

OTHER LABORATORY INVESTIGATIONS

Complete blood cell count, urine analysis, and serum alanine aminotransferase (ALT), blood urea nitrogen, and serum creatinine concentrations were determined before treatment and 24 hours later.

Results

STUDY POPULATION

A total of 122 patients were initially enrolled in the study; those in each treatment group were comparable for age, weight, and sexual exposure. Since penicillinase production of the infecting strain could not be determined from the pretreatment culture at the time of the patient's inclusion into the study, the patients were not grouped according to this criterion. Thus, using random allocation, it was solely by chance that more patients with PPNG strains were assigned to the cefaclor treatment group.

Twelve patients, including four given cefaclor and eight given ampicillin, were excluded from the study because of negative pretreatment culture results. Interestingly, in one such patient given cefaclor with a negative pretreatment culture result, post-treatment cultures from the cervix and rectum subsequently gave a heavy growth of PPNG. Despite the precautions taken against reinfection during the study, this could not be totally excluded, as the patient may have left the clinic without the knowledge of the clinic staff.

The ages of the remaining 110 patients ranged from 15 to 34 years with a mean of 20 years, and weights ranged from 36.3 kg to 61.3 kg with a mean of 45.5 kg. Thirty-eight of 110 (34.5%) patients were symptomatic; 44 patients were infected with PPNG and 66 with non-PPNG strains of *N gonorrhoeae*. Twenty-seven of the former and 30 of the latter were treated with cefaclor and the remainder received ampicillin.

TABLE I Results of treatment in 122 patients with uncomplicated gonococcal infection

| Treatment outcome | No of patients harbouring strains of: | | |
|----------------------|---------------------------------------|----------|-------|
| | PPNG | Non-PPNG | Total |
| Cefaclor (n = 61)* | | | |
| Response | 27 | 26 | 53 |
| Failure | 0 | 4 | 4 |
| Total | | | 57 |
| Ampicillin (n = 61)* | | | |
| Response | 1 | 36 | 37 |
| Failure | 16 | 0 | 16 |
| Total | | | 53 |

*Of the two treatment groups, four and eight patients were excluded from the analysis as their pretreatment culture results were negative for *N gonorrhoeae*.

PPNG = penicillinase-producing *N gonorrhoeae*; n = No of patients treated

TREATMENT

Fifty-three of the 57 (93%) patients treated with cefaclor responded to treatment compared with 37 of 53 (69.8%) patients treated with ampicillin. This difference was statistically significant ($\chi^2_1 = 8.416$, $P < 0.01$). Of patients with PPNG infections, all 27 responded to cefaclor while 16 of 17 (94.1%) failed to respond to ampicillin (table I). The single patient who responded to ampicillin had only a few colonies of PPNG in her pretreatment culture from the urethra; after treatment no organisms were cultured from this site. In patients with non-PPNG infections the therapeutic response was significantly better with ampicillin ($P = 0.038$ by Fisher's exact test) since no failure was noted with this drug compared with four failures out of 30 (13.3%) with cefaclor.

MINIMUM INHIBITORY CONCENTRATIONS

The correlation between the treatment response with cefaclor and the corresponding MICs of cefaclor for the infecting strains are shown in table II. Four treatment failures occurred among patients infected with

TABLE II Minimum inhibitory concentrations of infecting *N gonorrhoeae* strain from patients treated with cefaclor in relation to treatment failures

| MIC ($\mu\text{g/ml}$) | No of patients harbouring strains of: | | | |
|--------------------------|---------------------------------------|--------|----------|--------|
| | PPNG | | Non-PPNG | |
| | Treated | Failed | Treated | Failed |
| ≤ 0.025 | 1 | 0 | | |
| 0.1 | 3 | 0 | 4 | 1 |
| 0.2 | | | 7 | 0 |
| 0.5 | 15 | 0 | 14 | 1 |
| 1.0 | 6 | 0 | 4 | 2 |
| ≥ 2.0 | | | 1 | 0 |
| ND | 2 | 0 | 0 | 0 |
| Total | 27 | 0 | 30 | 4 |

PPNG = penicillinase-producing *N gonorrhoeae*; ND = not done

non-PPNG strains; of these, two had MICs of 1.0 µg/ml, one of 0.5 µg/ml, and one of 0.1 µg/ml. Two of 25 (8%) patients whose infecting strains had MICs of ≤ 0.5 µg/ml cefaclor failed to respond compared with two of five (40%) with MICs of ≥ 1.0 µg/ml cefaclor; this difference was not statistically significant ($P = 0.019$ by Fisher's exact test). Sixteen patients who failed to respond to ampicillin had infecting strains of PPNG with MICs ranging from 4.0– ≥ 64 µg/ml of ampicillin.

The MICs of cefaclor, ampicillin, and penicillin for the isolates are shown in table III. The MICs of the three antibiotics were not determined in a few of the isolates, which could not be retrieved from the stock cultures. The MIC range of cefaclor for PPNG strains was 0.01–1.0 µg/ml with 84.2% of isolates inhibited by 0.5 µg/ml and was similar to that for non-PPNG strains at 0.005–2.0 µg/ml with 87.1% of isolates inhibited by 0.5 µg/ml. Cefaclor was slightly more active in vitro than ampicillin and penicillin against non-PPNG strains; the ampicillin MIC range was 0.05–8.0 µg/ml with 79% of isolates inhibited by 0.5 µg/ml while the penicillin MIC range was 0.01–4.0 µg/ml with 75.4% of isolates inhibited by 0.5 µg/ml. The PPNG strains were uniformly resistant to ampicillin and penicillin with MIC ranges of 4.0– ≥ 64 µg/ml and 16.0– ≥ 64 µg/ml respectively.

SIDE EFFECTS

Three of 57 (5.3%) patients given cefaclor had side effects of dizziness (one) and dizziness, headache,

TABLE III Cumulative percentage of isolates inhibited by increasing concentrations of cefaclor, ampicillin, and penicillin

| MIC (µg/ml) | % of isolates inhibited by: | | | | | |
|----------------|-----------------------------|----------|------------|----------|------------|----------|
| | Cefaclor | | Ampicillin | | Penicillin | |
| | PPNG | Non-PPNG | PPNG | Non-PPNG | PPNG | Non-PPNG |
| ≤ 0.005 | | 1.6 | | | | |
| 0.01 | 2.6 | 1.6 | | | | 7.7 |
| 0.02 | 5.3 | 4.8 | | | | 10.8 |
| 0.05 | 5.3 | 11.3 | | 6.4 | | 26.2 |
| 0.1 | 31.6 | 38.7 | | 37.1 | | 33.8 |
| 0.2 | 36.8 | 58.1 | | 64.5 | | 46.2 |
| 0.5 | 84.2 | 87.1 | | 79.0 | | 75.4 |
| 1.0 | 100 | 98.4 | | 95.2 | | 87.7 |
| 2.0 | | 100 | | 98.4 | | 95.4 |
| 4.0 | | | 2.7 | 98.4 | | 100 |
| 8.0 | | | 8.1 | 100 | | |
| 16.0 | | | 21.6 | | 8.1 | |
| 32.0 | | | 40.5 | | 43.2 | |
| ≥ 64.0 | | | 100 | | 100 | |
| No tested | 38 | 62 | 37 | 62 | 37 | 65 |
| No not tested* | 6 | 4 | 7 | 4 | 7 | 1 |

*Isolates not retrieved from stock cultures for MIC determination
PPNG = penicillinase-producing *N. gonorrhoeae*

and nausea (two). In contrast, only one of 53 (1.9%) patients given ampicillin complained of dizziness. Ten patients treated with cefaclor showed changes in blood analysis (eosinophilia in six, leucopenia in two, leucocytosis in one, and a mildly raised ALT concentration in one) compared with 14 treated with ampicillin (eosinophilia in seven, leucopenia in three, leucocytosis in two, and a mildly raised ALT concentration in two).

Discussion

With the recently reported isolation of a spectinomycin-resistant strain of PPNG⁸ an appraisal of the efficacy of the cephalosporins as an alternative treatment for gonococcal infection has become imperative. Despite earlier discouraging results of the treatment of gonorrhoea with older cephalosporins, such as cephaloridine, cefazolin, and cephalexin,⁹⁻¹² newer congeners (notably cefuroxime and cefamandole) and a cephamycin, cefoxitin, have shown excellent in-vitro activity against *N. gonorrhoeae*.¹³ Cefuroxime and cefoxitin have been highly effective in the treatment of gonococcal infections, including those due to PPNG.^{4,14} In addition to these drugs, our study shows that cefaclor, an oral cephalosporin, has excellent in-vitro activity against *N. gonorrhoeae* and was effective at a dose of 3 g in the treatment of uncomplicated gonococcal infections in women particularly those due to PPNG. Its oral route of administration is an important advantage over cefuroxime and cefoxitin, which may make it more acceptable to patients. As empirical treatment before the results of tests for penicillinase production of the infecting strain were known, cefaclor was more efficacious than ampicillin (93% responded to cefaclor compared with 69.8% to ampicillin). This significant difference ($\chi^2_1 = 8.416$, $P < 0.01$) is attributed to the 40% incidence of PPNG infections in the patients studied. As expected, such patients responded poorly to β -lactamase-sensitive drugs like ampicillin and penicillin.

The treatment failure rate among patients infected with non-PPNG strains was 13.3% with cefaclor compared with zero failure with ampicillin. In-vitro data suggest that cefaclor should be as effective as ampicillin, so that the significant difference ($P = 0.038$ by Fisher's exact test) in the treatment results might be attributed to differences in the pharmacokinetics of the two drugs, most likely enhanced by the concomitant administration of probenecid with ampicillin. Pharmacokinetic studies indicate that while cefaclor is rapidly absorbed in the gastrointestinal tract, it is cleared more rapidly than cephalexin from the serum¹⁵ and has a half-life of 0.76 hours after a 1-g dose with no detectable con-

centrations six hours later.¹⁶ Conceivably, probenecid given with cefaclor in the treatment of gonococcal infection may ensure higher and prolonged concentrations of cefaclor. This potential benefit remains to be determined.

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